

**PRELIMINARY AMENDMENT**

Serial Number: 09/634207

Filing Date: August 9, 2000

Title: INDOLE COMPOUNDS USEFUL FOR THE TREATMENT OF CANCER

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Page 8

**REMARKS**

Claims 50-54 are added, and claims 10 and 49 are amended. Claims 10, 12-23 and 49-54 are now pending in this application. the amendments to the specification and claims are to clarify the subject matter that applicants regard as their invention. No new subject matter is added.

The Examiner is invited to telephone Applicants attorney listed below to discuss any questions which may remain with respect to the present application.

Respectfully Submitted,

DENNIS A. CARSON ET AL.

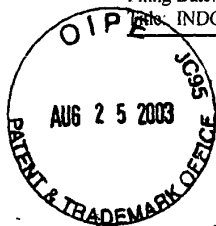
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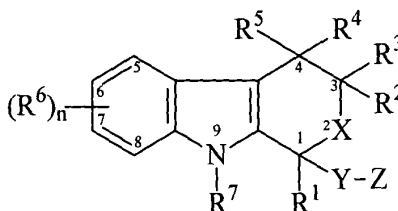
IN THE SPECIFICATION

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Please amend the specification as follows:

Please amend the paragraph at page 3, line 15 to page 4, line 4 as follows:

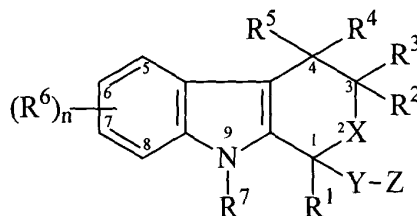
The present invention provides indole compounds of formula (I):



wherein  $R^1$  is lower alkyl, lower alkenyl, (hydroxy)lower alkyl, lower alkynyl, phenyl, benzyl or 2-thienyl,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and are each hydrogen or lower alkyl; each  $R^6$  is individually hydrogen, lower alkyl, hydroxy, (hydroxy)lower alkyl, lower alkoxy, benzyloxy, lower alkanoyloxy, nitro or halo,  $n$  is 1-3,  $R^7$  is hydrogen, lower alkyl or lower alkenyl,  $X$  is oxy and thio,  $Y$  is carbonyl,  $(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}C(O)$ , or  $(CH_2)_{1-3}SO_2$  and  $Z$  is  $(\omega-(4\text{-pyridyl})(C_2\text{-}C_4\text{ alkoxy}))$ ,  $(\omega-((R^8)(R^9)\text{ amino})(C_2\text{-}C_4\text{ alkoxy}))$ , wherein  $R^8$  and  $R^9$  are each H,  $(C_1\text{-}C_3)\text{ alkyl}$  or together with N are a 5- or 6-membered heterocyclic ring comprising 1-3  $N(R^8)$ , S or nonperoxide O; an amino acid ester of  $(\omega-(HO)(C_2\text{-}C_4)\text{ alkoxy}, N(R^8)CH(R^8)CO_2H, \underline{OCH_2CH_2N(CH_3)_3^+}$ , or 1'-D-glucuronyloxy; or  $Y-Z$  is  $(CH_2)_{1-3}R^{10}$  wherein  $R^{10}$  is OH,  $(C_2\text{-}C_4)\text{ acyloxy}$ ,  $SO_3H$ ,  $PO_4H_2$ ,  $N(NO)(OH)$ ,  $SO_2NH_2$ ,  $PO(OH)NH_2$ ,  $[\underline{OCH_2CH_2N(CH_3)_3^+}]$  or tetrazolyl; or a pharmaceutically acceptable salt thereof.

Please amend the paragraph at page 8, lines 5 to 23, as follows:

Indole compounds of the present inventions include compounds of formula (I):



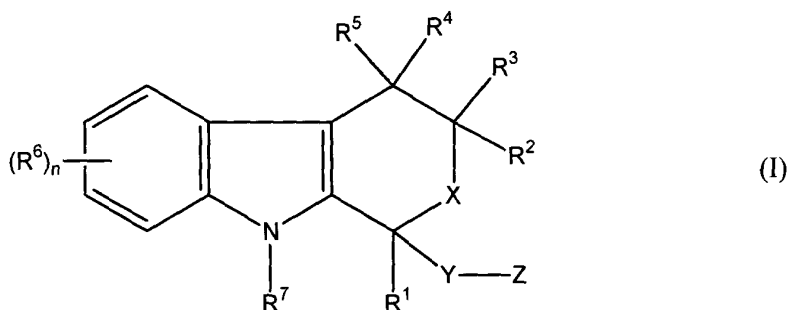
wherein  $R^1$  is selected from the group consisting of lower alkyl, lower alkenyl, (hydroxy)lower alkyl, lower alkynyl, phenyl, benzyl and 2-thienyl,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and are each selected from the group consisting of hydrogen and lower alkyl, each  $R^6$  is individually selected from the group consisting of hydrogen, lower alkyl, hydroxy, (hydroxy)lower alkyl, lower alkoxy, benzyloxy, lower alkanoyloxy, nitro and halo,  $n$  is 1-3,  $R^7$  is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl,  $X$  is selected from the group consisting of oxy and thio,  $Y$  is selected from the group consisting of carbonyl  $(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}SO_2$  or  $(CH_2)_{1-3}C(O)$ , and  $Z$  is selected from the group consisting of hydroxy, lower alkoxy optionally substituted with OH, 4-pyridyl, amino, lower alkylamino, di(lower alkyl)amino,  $[[\text{O}]]$   $OCH_2CH_2N(CH_3)_3^+$ , N-morpholino; amino, lower alkylamino,  $[(\text{carboxy})(\text{lower alkyl})]$ amino, di(lower)alkylamino and phenylamino, or  $Y-Z$  is  $(CH_2)_{1-3}R^{10}$  wherein  $R^{10}$  is OH,  $(C_2-C_4)$ acyloxy,  $SO_3H$ ,  $PO_4H_2$ ,  $N(NO)(OH)$ ,  $SO_2NH_2$ ,  $PO(OH)NH_2$ ,  $OCH_2CH_2N(CH_3)_3^+$ , or tetrazolyl or a pharmaceutically acceptable salt thereof. Lower alkyl, alkenyl, alkanoyl, etc. indicates a branched, cyclic or straight chain  $C_1-C_6$  group, preferably a  $C_1-C_4$  group, including cycloalkyl and (cycloalkyl)alkyl. (Hydroxy)lower alkyl or alkoxy is preferably 1- or 2-hydroxyethyl.

IN THE CLAIMS

Please amend claims 1, 49, and add claims 50-56 as follows:

Claims 1-9 Cancelled

10. (Currently amended) A method of treating leukemia, multiple myeloma or prostate cancer in a mammal comprising administering an effective amount of a compound of formula (I):



wherein  $R^1$  is lower alkyl, lower alkenyl, (hydroxy)lower alkyl, lower alkynyl, phenyl, benzyl or 2-thienyl,

$R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and are each hydrogen or lower alkyl;

each  $R^6$  is individually hydrogen, lower alkyl, hydroxy, (hydroxy)lower alkyl, lower alkoxy, benzyloxy, lower alkanoyloxy, nitro or halo,  $n$  is 1-3,

$R^7$  is hydrogen, lower alkyl or lower alkenyl,

$X$  is oxy or thio,

$Y$  is carbonyl,  $(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}SO_2$  or  $(CH_2)_{1-3}C(O)$ , and

$Z$  is ( $\omega$ -(4-pyridyl)( $C_2$ - $C_4$ alkoxy), ( $\omega$ -(( $R^8$ )( $R^9$ ) amino)( $C_2$ - $C_4$  alkoxy), [~~wherein  $R^8$  and  $R^9$  are each H, ( $C_1$ - $C_2$ )alkyl or together with N, are a 5- or 6-membered heterocyclic ring having 1-3 N( $R^8$ ), S or nonperoxide O;~~] an amino acid ester of ( $\omega$ -(HO)( $C_2$ - $C_4$ )alkoxy, N( $R^8$ )CH( $R^8$ )CO<sub>2</sub>H, 1'-D-glucuronyloxy, [~~OH, ( $C_2$ - $C_4$ )acyloxy, SO<sub>3</sub>H, PO<sub>4</sub>H<sub>2</sub>, N(NO)(OH), SO<sub>2</sub>NH<sub>2</sub>, PO(OH)(NH<sub>2</sub>);]~~] or OCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>3</sub><sup>+</sup> [~~amino, lower~~

~~alkylamino, di(lower alkyl)amino, phenylamino, or tetrazolyl]];~~

wherein R<sup>8</sup> and R<sup>9</sup> are each H, (C<sub>1</sub>-C<sub>3</sub>)alkyl or together with N, are a 5- or 6-membered heterocyclic ring having 1-3 N(R<sup>8</sup>), S or nonperoxide O; or

Y-Z is (CH<sub>2</sub>)<sub>1-3</sub>R<sup>10</sup> wherein R<sup>10</sup> is OH, (C<sub>2</sub>-C<sub>4</sub>)acyloxy, SO<sub>3</sub>H, PO<sub>4</sub>H<sub>2</sub>, N(NO)(OH), SO<sub>2</sub>NH<sub>2</sub>, PO(OH)NH<sub>2</sub>, or tetrazolyl;

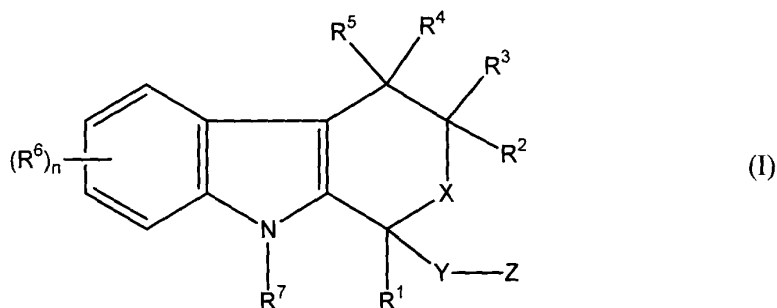
or a pharmaceutically acceptable salt thereof; to a mammal afflicted with leukemia, multiple myeloma or prostate cancer.

11. Cancelled.
12. (Previously presented) The method of claim 10 wherein the treatment is for prostate cancer.
13. (Previously presented) The method of claim 10 wherein the treatment is for multiple myeloma.
14. (Previously presented) The method of claim 10 wherein the leukemia is chronic lymphocytic leukemia.
15. (Previously presented) The method of claim 10 wherein the compound of formula I is administered orally.
16. (Original) The method of claim 15 wherein an enterically coated dosage form is administered.
17. (Previously presented) The method of claim 10 wherein the compound of formula (I) is administered parenterally.
18. (Previously presented) The method of claim 10 wherein the compound of formula (I) is administered in combination with a chemotherapeutic agent.

19. (Previously presented) The method of claim 12 wherein the compound of formula (I) is administered in combination with a chemotherapeutic agent.
20. (Previously presented) The method of claim 18 wherein the chemotherapeutic agent is mitoxantrone, prednisone, estramustine, melphalan, vinblastine or a combination thereof.
21. (Original) The method of claim 19 wherein the chemotherapeutic agent is an anti-androgen.
22. (Original) The method of claim 21 wherein the anti-androgen is bicaftamide, nilutamide, flutamide, cycloproterone acetate or a combination thereof.
23. (Original) The method of claim 21 wherein the anti-androgen is leuprolide acetate, goserelin acetate or a combination thereof.

Claims 24-48 cancelled.

49. (Currently amended) A method of treating hematopoietic cancers, cancers of the bone marrow, and cancers that express high levels of PPAR- $\gamma$  in a mammal comprising administering an effective amount of a compound of formula (I):



wherein  $R^1$  is lower alkyl, lower alkenyl, (hydroxy)lower alkyl, lower alkynyl, phenyl, benzyl or 2-thienyl,

$R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are the same or different and are each hydrogen or lower alkyl;

each  $R^6$  is individually hydrogen, lower alkyl, hydroxy, (hydroxy)lower alkyl, lower

alkoxy, benzyloxy, lower alkanoyloxy, nitro or halo, n is 1-3,

$R^7$  is hydrogen, lower alkyl or lower alkenyl,

X is oxy or thio,

Y is carbonyl,  $(CH_2)_{1-3}$ ,  $(CH_2)_{1-3}SO_2$  or  $(CH_2)_{1-3}C(O)$ , and

Z is ( $\omega$ -(4-pyridyl)( $C_2$ - $C_4$ alkoxy), ( $\omega$ -(( $R^8$ )( $R^9$ ) amino)( $C_2$ - $C_4$  alkoxy), [~~wherein  $R^8$  and  $R^9$  are each H, ( $C_1$ - $C_3$ )alkyl or together with N, are a 5- or 6-membered heterocyclic ring having 1-3 N( $R^8$ ), S or nonperoxide O;~~] an amino acid ester of ( $\omega$ -(HO)( $C_2$ - $C_4$ )alkoxy, N( $R^8$ )CH( $R^8$ )CO<sub>2</sub>H, 1'-D-glucuronyloxy, [~~OH, ( $C_2$ - $C_4$ )acyloxy, SO<sub>3</sub>H, PO<sub>4</sub>H<sub>2</sub>, N(NO)(OH), SO<sub>2</sub>NH<sub>2</sub>, PO(OH)(NH<sub>2</sub>);~~] or OCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>3</sub><sup>+</sup> [~~amino, lower alkylamino, di(lower alkyl)amino, phenylamino, or tetrazolyl~~];

wherein  $R^8$  and  $R^9$  are each H, ( $C_1$ - $C_3$ )alkyl or together with N, are a 5- or 6-membered heterocyclic ring having 1-3 N( $R^8$ ), S or nonperoxide O; or

Y-Z is  $(CH_2)_{1-3}R^{10}$  wherein  $R^{10}$  is OH, ( $C_2$ - $C_4$ )acyloxy, SO<sub>3</sub>H, PO<sub>4</sub>H<sub>2</sub>, N(NO)(OH), SO<sub>2</sub>NH<sub>2</sub>, PO(OH)NH<sub>2</sub>, or tetrazolyl;

or a pharmaceutically acceptable salt thereof; to a mammal afflicted with hematopoietic cancer, cancer of the bone marrow, and cancer that expresses a high level of PPAR- $\gamma$ .

50. (New) The method of claim 49 wherein the treatment is for hematopoietic cancer.
51. (New) The method of claim 49 wherein the treatment is for cancer of the bone marrow.
52. (New) The method of claim 49 wherein the treatment is for cancer that expresses a high level of PPAR- $\gamma$ .
53. (New) The method of claim 49 wherein the compound of formula I is administered orally.
54. (New) The method of claim 49 wherein an enterically coated dosage form is administered.